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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/305,390	05/05/99	YAMAMOTO H	06501/030001

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EXAMINER	
HUTSON,R	
ART UNIT	**PAPER NUMBER**
1652	18

DATE MAILED: 11/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/305,390	Yamamoto
Examiner	**Group Art Unit**
Richard Hutson	1652

☒ Responsive to communication(s) filed on Aug 15, 2000

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 7-10, 12, 14, and 23-27 is/are pending in the applicat

Of the above, claim(s) 25-27 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 7-10, 12, 14, 23, and 24 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Cancellation of claims 1-6, 11, 13 and 16-22 and the amendment of claims 7-10 and the addition of claims 23-27 is acknowledged. Claims 7-10, 14, and 23-27 are at issue and are present for examination.

Applicants' arguments filed on 8/15/2000, paper No. 15, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Election/Restriction

1. Newly submitted claims 25-27 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Inventions of elected group II and the invention of claims 25-27 are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions utilize different products. Elected group II utilizes an acetoacetyl CoA reductase protein whereas newly added claims 25-27 utilize a nucleic acid encoding an acetoacetyl CoA reductase.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 25-27 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 7-10, 12, 14 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with a **naturally occurring acetoacetyl-CoA reductase**, does not reasonably provide enablement for a method for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with **any** protein capable of reducing 4-halo-acetoacetic acid ester or its derivative to produce (S)-4-halo-3-hydroxybutyric acid ester. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

This rejection was explained in the previous office action as previously applied to claims 7-10, 12, 14 and 19-22.

Applicant traverses this rejection on a number of different basis. First applicant asserts that the examiner states the claims are drawn to a method comprising using any protein. This argument is not found persuasive, because the examiner throughout the rejection referred to "any protein capable of reducing 4-halo-aceteoacetic acid ester or its derivative", not "any protein" (See page 3, lines 7-8).

Second applicants argument that the specification is enabling for the use of naturally occurring acetoacetyl CoA reductases and their fusion proteins is convincing, and applicants are reminded that the currently rejected claims are not drawn to methods of using naturally occurring acetoacetyl CoA reductases but rather "any protein having acetoacetyl-CoA reductase activity".

Third the applicants asserts the claims are enabled because not only are the methods of producing mutant enzymes routine in the art, but that the specification provides specific methods that can be used to generate mutants along with functional assays. This is not persuasive because while methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., methods comprising an acetoacetyl CoA reductase) requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without effecting -acetoacetyl CoA reductase activity; (B) the general tolerance of -acetoacetyl CoA reductases to modification and extent of such tolerance;

(C) a rational and predictable scheme for modifying any -acetoacetyl CoA reductase residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Further it is noted that a method using a protein derived from a specific microorganism is interpreted as including said method using both natural and non-natural variants of said protein.

4. Claims 7-10, 12, 14, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is stated in the previous office action as it was previously applied to claims 7-10, 12, 14 and 19-22.

Claims 7-10, 14, 23 and 24 are directed to all possible methods for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with **all possible** "proteins capable of reducing 4-halo-acetoacetic acid ester or its derivative to produce (S)-4-halo-3-hydroxybutyric acid ester". The specification, however, only provides a method for producing (S)-4-halo-3-hydroxybutyric acid ester comprising asymmetrically reducing 4-halo-acetoacetic acid ester or its derivative with a single representative species of acetoacetyl-CoA reductase, i.e. that corresponding to SEQ ID NO: 9, encompassed by these claims.

Applicant traverses this rejection as above on the basis that the examiner has failed to appreciate the applicants invention in not realizing that the pending claims are limited to the use of an acetoacetyl CoA reductase rather than "any protein". As above this argument is not found persuasive for the reasons stated above.

Applicant further traverses this argument on the basis that 20 examples of acetoacetyl CoA reductases from a diverse array of organisms can be used in the methods of the invention. This argument as is persuasive in that the description of said method of use of the 20 naturally occurring acetoacetyl CoA reductases is adequately described. The basis of this description is the known structure of the 20 disclosed acetoacetyl reductase, and the common functional characteristic of each of these naturally occurring species, being capable of acetoacetyl CoA reductase activity. Applicant is reminded as above under the scope of enablement rejection that the currently amended claims read on methods of use of non-naturally occurring variants of acetoacetyl CoA reductase and are therefore rejected under this section.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is indefinite in the recitation of "stringent conditions" as the specification does not define what conditions constitute "stringent". There is nothing to suggest the limits of those conditions that would be included within the scope of this term and in the art what is considered stringent varies widely depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a gene encoding SEQ ID NO: 10, a sequence must be to be included within the scope of these claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 7-10, 14, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuyama et al. (U.S. Patent No.: 5,559,030) in view of Peoples et al. (U.S. Patent No.: 5,229,279) or Summerville et al. (WO 93/02187).

The rejection is stated in the previous office action as it applied to claims 8, 9, 14, 20, 21 and 22.

The applicant traverses this rejection on the basis that there is no motivation whatsoever to combine an acetoacetyl CoA reductase (as described by Peoples or Summerville) with a method of asymmetrically reducing a 4-halo-acetoacetic acid ester (as described in Matsuyama).

As stated in the previous office action, the motivation in using the acetoacetyl-CoA reductases of Peoples et al. or Summerville et al. is that the nucleic acids encoding these enzyme have been cloned and therefore this allows for more control in the reaction conditions and the opportunity to improve the enzyme by the use of recombinant technologies and mutagenesis. Further the motivation for the combination of the Peoples et al. or Summerville et al. references with the Matsuyama et al. reference is that each of the references involves the reduction of acetoacetic acid or its derivative to hydroxybutyrate or its derivative and one of ordinary skill in the art would expect that the same enzyme would be responsible for such a conversion irregardless of the presence of an extraneous halogen group. With respect to newly added claim 23, Peoples et al. also teach the isolation of the gene encoding acetoacetyl reductase from *Zoogloea ramigera* and therefore this claim is also included in this rejection.

Therefore, claims 7-10, 14, 23 and 24 are made obvious by Matsuyama et al,. Peoples et al. and Summerville et al.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on M-F from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy (Murthy), can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson Ph.D.
10/31/2000

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